Received:
06 March 2018

Revised:
04 April 2019

Accepted:
10 April 2019

<https://doi.org/10.1259/bjr.20180233>

Cite this article as:

Mitsumoto T, Minamimoto R, Sunaoka F, Kishimoto S, Inoue K, Fukushi M. The clinical utility of phase-based respiratory gated PET imaging based on visual feedback with a head-mounted display system. *Br J Radiol* 2019; **92**: 20180233.

FULL PAPER

The clinical utility of phase-based respiratory gated PET imaging based on visual feedback with a head-mounted display system

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Objective: We developed a new respiratory-gated positron emission tomography (PET) imaging method (RGV-PET) that phase-based respiratory gated PET imaging (RG-PET) combine with head-mounted display (HMD)-guided “visual feedback.” The purpose of this study was to investigate whether RGV-PET is effective at improving the quantitative measurement of tracer uptake in tumors using the phase-based respiratory gating method.

Methods: Of the 41 enrolled patients with hepatobiliary or pancreatic cancer, 20 patients underwent RGV-PET and the remaining 21 patients underwent RG-PET. We measured the peak standardized uptake value (SUVpeak) of the primary lesion in each five bins obtained from both RG-PET and RGV-PET. The SUVpeak change rate calculated based on the ungated PET imaging. To evaluate the quantitative variation, the coefficient of variation of the SUVpeak change rate was compared between

RG-PET and RGV-PET. In addition, we performed qualitative evaluation using visual score for the incidence of artifacts on four-dimensional-CT.

Results: The coefficient of variation of the average SUVpeak change rate in RGV-PET was 7.01 ± 4.43 , which was significantly lower than the values in RG-PET (10.72 ± 5.74 , $p < 0.05$). A significant improvement in the SUVpeak change rate of RGV-PET was obtained in bins 1 and 2 compared to RG-PET ($p < 0.05$). The visual score of RGV-PET was significantly lower than RG-PET ($p < 0.05$).

Conclusion: RGV-PET was effective for respiratory stabilization and improved respiratory gating imaging quality.

Advances in knowledge: The RGV-PET is applicable to various PET/CT respiratory gating imaging and may improve the quantitateness of PET images.

INTRODUCTION

Respiratory motion, especially in the thorax and abdominal regions, is a factor that potentially reduces the image quality and quantitative accuracy of lesions on positron emission tomography (PET)/CT.¹ The recent respiratory motion correction techniques on PET/CT, including respiratory-gated PET;² respiratory-correlated dynamic PET;³ and deep-inspiration breath-hold PET;^{4,5} enable synchronization of PET and CT acquisition with respiratory motion and have high potential for improving the image quality of moving lesions in the body.

Respiratory-gated PET technique has two major methods, the phase-based gating and amplitude-based gating. In phase-based respiratory gated PET imaging (RG-PET), the respiratory cycle is divided into multiple phase bins using four-dimensional CT (4D-CT) and the acquired data

are classified into each phase range based on the acquisition time within the breathing cycle. On the other hand, amplitude-based RG-PET imaging uses the stable expiratory phase of breathing, thereby, suppressing the radiation exposure dose by skipping 4D-CT scan. Also, unlike phase-based gating, amplitude-based gating cannot evaluate all respiratory phases because it uses the respiratory phase (mainly expiratory phase) corresponding to the CT image obtained for attenuation correction.

Accuracy of CT attenuation correction is important for the quantitateness of respiratory-gated PET images. Particularly in RG-PET, the influence on quantitateness is large, and the attenuation-corrected image corresponding to each phase data depend on the accuracy of 4D-CT. RG-PET is the optimal method for patients who are breathing regularly, but its accuracy becomes less if a patient has irregular

and unstable breathing. In order to improve breath-hold compliance, an image-guided breath-hold technique was newly devised to provide respiratory-related feedback to patients through visual and/or auditory signals.^{6–8} Because respiration causes movement of internal organs and tumors in the thorax and abdomen, respiratory movement should be considered in radiation therapy. Also, when using PET images, accurate delineation of tumor lesions based on PET/CT is required in radiotherapy treatment planning. Head-mount display (HMD) is a key device for the visual feedback method and works by superimposing a visual information display over the wearer's field of view. The visual feedback method by HMD for CT imaging was reported to have advanced in terms of reducing fluctuations in wall motion and improving the reproducibility of gating.^{6,8–11} The technology surrounding HMD is advanced, and it is now widely applied to several fields, including medicine.^{12,13} Our hypothesis was that this visual feedback method using HMD will contribute in stabilizing breathing motion during RG-PET. Yang *et al* reported the use of audiovisual biofeedback system in PET imaging, but the research results did not provide a satisfactory effect.¹⁴ We hypothesized that simple training sessions on breathing with projection of individual patient's respiration using HMD might be a key component for improving the results. The purpose of this study was to investigate the efficacy of the new RG-PET method (RGV-PET) combined with RG-PET with HMD-guided "visual feedback" for stabilizing the quality and quantity of lesions on fludeoxyglucose (FDG)-PET/CT images, compared with RG-PET.

METHODS AND MATERIALS

Patient selection

This retrospective study was approved by the institutional review board of National Center for Global Health and Medicine, and informed consent was obtained from each patient. This study included patients who underwent FDG-PET/CT for initial staging of hepatobiliary or pancreatic cancer from May 2012 to January 2013. During routine clinical FDG-PET/CT exams, the patients were notified about the possibility of having an additional RG-PET or RGV-PET scan, in case the nuclear physician required additional RG-PET/CT for further evaluation of a lesion in the upper abdominal area. Lesions with a maximum diameter ≥ 20 mm on diagnostic CT scan were identified as the targets for PET/CT study. Patients who were unable to hear and/or understand instructions, complained of dyspnea, or had difficulty in undergoing an additional RG-PET or RGV-PET scan were excluded. If the target lesion did not have visually higher FDG uptake than that in the surroundings, additional RG-PET or RGV-PET scan was not performed. The final diagnosis was based on histologic assessment or clinical and radiologic follow-up after at least 6 months.

PET/CT scan

All PET data were collected on a Discovery PET/CT 600 scanner (GE Healthcare, Milwaukee, WI), which provided 47 planes and a 15.9 cm axial field of view with a system. RG-PET was performed using Varian Real-time Position Management Respiratory Gating System, (RPM, Varian Medical Systems, Palo Alto, CA). The RPM, an infrared camera that was mounted on the PET/CT table and an infrared-reflective marker block that was

fixed on the top of the phantom to make it visible to the camera at all times and enable continuous tracking of simulated respiratory motion.

All patients fasted for at least 6 h before the PET/CT studies. In all patients, the serum glucose level measured at the time of FDG injection was less than 160 mg/dl. FDG was intravenously administered at a dose of 5 MBq/kg body weight. Whole body PET/CT was performed from the vertex to the upper thigh using 3 min scans and 7–8 bed positions. After approximately 10–15 min from the end of whole body PET/CT scan, RG-PET or RGV-PET was performed using a single bed position.

Consecutive PET emission data were acquired for 10 min using the list mode scan. For the RG PET/CT scan, we implemented cine CT for attenuation correction with free breathing into the clinical workflow. The cine CT (4D-CT) was done with 0.5 s rotation, 2.5 mm slice, 15 mAs, and 120 kVp.

HMD-guided visual feedback

The RPM system can project the respiratory analysis screen on the monitor. [Figure 1](#) shows an overview of the RGV-PET system used in this study. The subvideo terminal of the RPM system in the control room was distributed to the patient's HMD (Wrap1200, Vuzix Corporation, Henrietta, NY, USA) in the examination room. During the respiratory training for HMD use, we informed the patients to breathe as they see the bar model rise and fall with respiration and that it should reflect the wave model as the locus of respiration. We repeated the instructions until the bar and wave models were considered constant by a nuclear technologist. For the RG-PET scan, the patients were generally instructed to keep constant voluntary breathing. The both RG-PET and RGV-PET scan were started when three successive amplitude and breathing periods were stable.

PET image reconstruction

All obtained PET and CT images were transformed to the AW work station 600 (GE Healthcare, Fairfield, CT) for image reconstruction. PET data were reconstructed using a 4.0 mm resolution with FWHM gaussian filter, a three-dimensional-ordered subset expectation maximization algorithm (3 iterations, 16 subsets), and an image matrix size of 192×192 pixels. For the standard reference, an ungated PET (UG-PET) image was reconstructed using the first 3 min of the 10 min of the list mode PET data. Both RG-PET and RGV-PET images were reconstructed from five bins (2 min/bin) of the list mode PET data under the phase gating method.¹⁵

Quantitative analysis

We extracted the breathing waveform from the RPM and calculated the value and coefficient of variance (CV) of both amplitude and breathing period by peak analysis (v. 9.1 OriginLab Corporation, Northampton, MA). This study was conducted for the purpose of stabilizing the quantitateness of each phase in phase-based gating. CV reflects the overall variability of each bin in the phase-based gating. A low CV indicates that the quantitateness is stable in every phase bin. Amplitude and breathing period are determined by the movement of the infrared-reflective

Figure 1. RGV imaging set-up The RPM system in the operation room is projected to the patient's HMD device with the use of the distributor in the examination room, so that the patient can recognize the RPM system. After explaining the significance of the examination, breathing training is repeated and RGV imaging is performed. HMD, head-mounted display.

marker block on the patient's abdomen. In other words, these are defined as the patient's abdomen displacement. The acquired PET image was divided into five time-stamped bins, each accounting for 20% of a breath cycle. These bins correlated with the phases of respiratory motion as Bin 1: early expiratory phase, Bin 2: middle expiratory phase, Bin 3: change from expiratory to inspiratory phase, Bin 4: early inspiratory phase, and Bin 5: middle to end of inspiratory phase. We measured the peak standardized uptake value (SUV_{peak}) of the lesion obtained from each of the five bins of both RG-PET and RGV-PET. SUV_{peak} is robust to image noise, it provides a more reliable metric compared to SUV_{max}.^{16–18} The lesion volume was defined SUV_{max} threshold of 42% on the UG-PET. The SUV_{peak} change rate of RG-PET and RGV-PET was compared with that of UG-PET and was calculated as follows:

$$\text{SUVpeak change rate} = \frac{\text{SUVpeak(RG-PET, RGV-PET)}}{\text{SUVpeak(UG-PET)}} \quad (1)$$

In order to evaluate the quantitative variation of the phase bins in the respiratory gating image, the average of the SUV_{peak} change rate among the five bins was calculated for individual patients, and compared between the RG-PET and RGV-PET cohorts. Thereafter, we also compared the CV of the average SUV_{peak} change rate between the RG-PET and RGV-PET cohorts. CV of the average SUV_{peak} change rate of RG-PET and RGV-PET was calculated as follows:

$$\text{CV(average SUVpeak change rate)} = \frac{1}{n} \sum_{i=1}^n \left[\frac{y_i}{x_i} \times 100 \right] \quad (2)$$

where “x” was defined as the mean SUV_{peak} value in the five bin, and “y” was defined as the standard deviation (SD) of SUV_{peak} values in the five bin and “n” was the patient number.

Next, we calculated the SUV_{peak} change rate in each bin between the RG-PET and RGV-PET cohorts in order to evaluate the phase bin that was most affected.

Finally, visual score (*vs*) was used to evaluate the images obtained by 4D-CT, which can have four types of artifacts (blurring, duplicate structure, overlapping structure, and incomplete structure).¹⁹ *vs* was categorized as 0: no artifact or 1: confirmed artifact. The rate of occurrence of these artifacts was compared between RG-PET and RGV-PET. 4D-CT images were reconstructed from the 3, 6, 9, and 12 bins, respectively; coronal sections of the images were scored for the presence or absence of 4D-CT artifacts in each bin by a blinded observer (nuclear medicine) using the AW work station 600 (GE Healthcare, Fairfield, CT, USA).

Statistical analysis

Data are presented as mean ± SD. RGV-PET and RG-PET were compared by the Student's *t*-test. The difference was assessed with two-side-test with an alpha level of 0.05. Statistical analysis was performed using IBM SPSS 21.0 for Windows (IBM COMPANY, Chicago, IL). *p* values less than 0.05 were considered statistically significant.

RESULTS

A total of 41 patients (17 males and 24 females; mean age: 70.1 ± 11.2 years) with hepatobiliary or pancreatic cancer (pancreatic cancer: 22, hepatocellular carcinoma: 5, liver metastases: 7, and cholangiocellular carcinoma: 7) were included in this study. As shown in Table 1, the characteristics of the enrolled patients were not significantly between the RG-PET and RGV-PET cohorts. As shown in Table 2, compared with RG-PET, RGV-PET had a similar amplitude (0.93 ± 0.44 cm *versus* 1.19 ± 0.88 cm, *p* = 0.55); significantly lower CV of amplitude (12.10 ± 4.27 *versus*

Table 1. Characteristics of patients and comparison between RG-PET and RGV-PET

Characteristics	RG-PET (N = 21)	RGV-PET (N = 20)	p-value
Age	69.7 ± 10.6	70.7 ± 11.6	0.97
BMI (kg/m ²)	20.9 ± 3.6	21.0 ± 3.0	0.74
SUVpeak (g/ml)	6.2 ± 2.7	5.5 ± 2.6	0.47
Volume* (cm ³)	14.1 ± 12.7	9.6 ± 4.9	0.25

BMI, body mass index; RG-PET, respiratory gated PET; SUVpeak, peak standardized uptake value.

Data are shown with mean ± standard deviation.

SUVpeak and volume were measured on ungated PET images.

Volume was defined as thresholded with 42% SUVmax in target lesions.

19.44 ± 10.54, $p < 0.05$); similar breathing period (5.74 ± 2.72 s *versus* 4.65 ± 1.09 s, $p = 0.63$); and significantly lower CV of breathing period (9.88 ± 3.53 *versus* 13.04 ± 4.34, $p < 0.05$).

Figure 2 shows the SUVpeak change rate in 41 cases enrolled in this study. RG-PET had many cases including phase bin where SUVpeak change rate is lower than one compared to RGV-PET.

Figure 3 shows that compared with RG-PET, RGV-PET had similar average SUVpeak change rates (1.13 ± 0.14 *vs* 1.19 ± 0.13, respectively; $p = 0.192$), but had significantly lower CV of the average SUVpeak change rates (10.72 ± 5.74 *vs* 7.01 ± 4.43, respectively; $p < 0.05$).

Table 3 shows that the SUVpeak change rate of RGV-PET improved in each bin compared with that of RG-PET. This improvement was prominent in bins 1 and 2, as manifested by the relatively large changes in respiratory waves, compared with bins 3 and 4, which had the quietest phase of the quiescent period. A significant improvement in the SUVpeak change rate was obtained in bins 1 and 2. Figure 4 represents RGV-PET image of each bin in patients with pancreatic cancer.

Figure 5 shows the differences in the *vs* in each bin between RG-PET and RGV-PET. For RG-PET, the respective *vs* and rate of occurrence of artifact were 0.52 ± 0.68 and 55% (11/20) in the 3 bins; 1.10 ± 1.14 and 65% (13/20) in the 6 bins; 1.76 ± 1.58 and 75% (15/20) in the 9 bins; and 2.86 ± 2.06 and 90% (18/20) in the 12 bins. For RGV-PET, the respective *vs* and rate of occurrence of artifact were 0 (no artifact) in the 3 bins; 0.20 ± 0.56 and 19.0% (4/21) in the 6 bins; 0.33 ± 0.62 and 28.6% (6/21) in the 9 bins; and 0.87 ± 1.36 and 42.9% (9/21) in the

12 bins. RGV-PET had significantly lower *vs* than RG-PET (all $p < 0.05$) and was effective in reducing the artifacts of 4D-CT.

DISCUSSION

We developed the RGV-PET that RG-PET combine with HMD, and showed that RGV-PET improved the CVs of breathing and SUVpeak change rates, compared with RG-PET, which enabled acquisition of PET images with stable respiration.

The usefulness of respiratory-gated imaging is the capability to suppress the reduction of the quantitative value of lesions caused by respiratory motion.^{20–22} In respiratory gating imaging, similar respiratory conditions in 4D-PET and 4D-CT can obtain accurate quantitative values because of highly accurate attenuation correction through reduction of image mismatch. However, the improvements in image quality²¹ and quantitative value (SUV) remain to be influenced by the stability of respiratory motion and the selected phase bin. For this reason, when respiratory motion is irregular during acquisition of 4D-CT data, respiratory sampling becomes less appropriate and the frequency of CT artifacts increases.¹⁹ In order to improve such conditions, respiratory motion needs to be managed by reducing irregularities within the respiratory cycle.

Yang et al studied the use of audiovisual biofeedback system which is a real-time, interactive and personalized system designed to help a patient self-regulate their breathing in PET imaging of a phantom²³ and of patients with lung cancer,¹⁴ and showed that audiovisual biofeedback system in RG-PET improved some, but not all, parameters among accuracy of the gross tumor volume, SUVmax, and 4D-CT images. They suggested that the system will work more effectively by optimizing the human–computer interface and including patient training sessions for improved comprehension and compliance. We hypothesized that it is effective to stabilize individual breathing of patients with simple breath training using HMD.

Our results showed that the RGV-PET system with simple training was effective for respiratory stabilization. The relatively higher trend for average SUVpeak change rate of RGV-PET than that of RG-PET was similar to the results presented by a previous report.¹⁴

However, as a result of analysis for each phase bin, significant improvement was obtained with SUVpeak change rate in bins 1 and 2. The slightly lower amplitude of RGV-PET than that of RG-PET would mainly work in the expiratory phase and would be less effective in the inspiratory phase, which was the quietest phase of the quiescent period.

Table 2. Comparison between RG-PET and RGV-PET in the amplitude and breathing period

Parameter	Level (mean ± SD)		p-value	CV value (mean ± SD)		p-value
	RG-PET	RGV-PET		RG-PET	RGV-PET	
Amplitude (cm)	1.19 ± 0.88	0.93 ± 0.44	0.55	19.44 ± 10.54	12.10 ± 4.27	$p < 0.05$
Breathing period (s)	5.74 ± 2.72	4.65 ± 1.09	0.63	13.04 ± 4.34	9.88 ± 3.53	$p < 0.05$

CV, co-efficient of variation; RG-PET, respiratory gated PET; SD, standard deviation.

Data are shown with mean ± standard deviation.

Figure 2. A box plot of the SUVpeak change rates of all phase bins in 41 cases. RG-PET, respiratory gated PET; SUVpeak, peak standardized uptake value.

Because respiration is known to be stable in the end-expiratory phase, the exhalation phase is usually selected for diagnosis during respiratory-gated imaging.^{1,20,21} Therefore, RGV-PET may be effective especially in bins 1 and 2 where breathing is irregular. On the other hand, the CVs of amplitude, breathing period, and average SUVpeak change rate

were significantly different between RG-PET and RGV-PET ($p < 0.05$). Furthermore, the quality of 4D-CT in RGV-PET was improved by reduction of artifacts.

The effectiveness of respiratory stabilization by visual feedback was reported in the field of radiotherapy using 4D-CT.^{24,25} In

Figure 3. A box plot of average SUVpeak change rates between RGV-PET and RG-PET. (a) The average SUVpeak change rate is not significantly different ($p = 0.192$) between the two cohorts. (b) On the other hand, the CV of the average SUVpeak change rate is significantly lower for RGV-PET than for RG-PET, and stable improvement is obtained. $*p < 0.05$. CV, coefficient of variation; HMD, head-mounted display; RG-PET, respiratory gated PET; SUVpeak, peak standardized uptake value.

Table 3. Comparison between RG-PET and RGV-PET in the SUVpeak change rate in each of phase bin

Phase bin	RG-PET (N = 21)	RGV-PET (N = 20)	p-value
1	1.05 ± 0.18	1.16 ± 0.14	<0.05
2	1.10 ± 0.15	1.21 ± 0.15	<0.05
3	1.19 ± 0.27	1.24 ± 0.23	0.58
4	1.17 ± 0.21	1.14 ± 0.11	0.58
5	1.13 ± 0.12	1.22 ± 0.15	0.28

RG-PET, respiratory gated PET; SUVpeak, peak standardized uptake value.

Data are shown with mean ± standard deviation. Phase bin 1: early expiratory phase, Phase bin 2: middle expiratory phase, Phase bin 3: change over from expiratory to inspiratory phase, Phase bin four early inspiratory phase, Phase bin 5: middle to end of inspiratory phase

general, in radiotherapy planning using 4D-CT, approximately 10 phase bins are been used in order to confirm the moving range and deformation shape of the lesion.²⁶ When using PET images with radiotherapy, a longer PET scan time is required as the number of phase bins increases, and may induce irregular breathing and degrade image quality. Previous studies reported that visual feedback could reduce respiratory irregularity and was effective for improvement of 4D-CT image quality.⁸⁻¹⁰ Also in this study, RGV-PET was more effective than RG-PET in suppressing 4D-CT artifacts which are factors that cause errors in PET attenuation correction. Thus, when many phase bins are required for reference images in radiation therapy, RGV-PET is expected to be effective.

Furthermore, RGV-PET may be able to reduce radiation exposure in 4D-CT scans. The exposure time for respiration sampling of a 4D-CT scan is generally performed by adding 0.5 s etc. to the patient's breathing period.²⁰ However, an irregular breathing

Figure 5. A linear plot showing the relationship between the phase bins and vs The occurrence of 4D-CT artifacts increases as the number of bins increases. RGV-PET reduces the frequency of artifacts and improves the quality of 4D-CT. Data are presented as mean ± SE. 4D-CT, four-dimensional CT; RG-PET, respiratory gated PET; SE, standard error.

period can lead to sampling of an insufficient breathing period and an increase in radiation exposure time. Patients with unstable respiration can rescue breathing by visual feedback with HMD and perform the examination by reasonable constant breathing.

Since RGV-PET is a simple system, it can be constructed at low cost and setup can be easily implemented by only mounting HMD to patients. The examination time of RGV-PET is also unchanged compared to RG-PET. Moreover, patients can adjust to the system after a simple explanation and a brief training on breathing, and could be applied to various respiratory-gated imaging.

Figure 4. RGV-PET maximum intensity projection images image of each phase bin in patients with pancreatic cancer. (No.11) * is SUVpeak change rate. RGV-PET improved SUVpeak compared to UG-PET, and high SUVpeak change rate was obtained in all phase bins. RG-PET, respiratory gated PET; SUVpeak, peak standardized uptake value.

STUDY LIMITATIONS

Some limitations of this study were the small number of cases and the fact that the patients were not evaluated for lung lesions. In addition, the exact improvement with RGV-PET was difficult to verify because the case was not the same patient in consideration of the exposure dose in this case study. Regarding 4D-CT, we evaluated the presence or absence of artifacts but did not evaluate the image quality. The reason is that 4D-CT was used only for attenuation correction, CT exposure was low dose. Nevertheless, the effectiveness of RGV-PET cannot be discounted because the improvements were obtained in cases with similar characteristics.

CONCLUSIONS

RGV-PET was effective in stabilizing respiration by significantly reducing variations in amplitude and breathing period, as well as the 4D-CT artifacts. The presents study showed the potential of RGV-PET for respiratory gating imaging with high reproducibility and stability.

ACKNOWLEDGMENT

This study was funded by a grant from the National Center for Global Health and Medicine (22S11903), Japan.

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